A Risk-benefit Analysis of Prophylactic Anticoagulation for Patients with Metastatic Germ Cell Tumours Undergoing First-line Chemotherapy

Fankhauser, Christian Daniel ; Tran, Ben ; Pedregal, Manuel ; Ruiz-Morales, José Manuel ; Gonzalez-Billalabeitia, Egon ; Patrikidou, Anna ; Amir, Eitan ; Seidel, Christoph ; Bokemeyer, Carsten ; Hermanns, Thomas ; Rumyantsev, Alexey ; Tryakin, Alexey ; Brito, Margarida ; Fléchon, Aude ; Kwan, Edmon M ; Cheng, Tina ; Castellano, Daniel ; Del Muro, Xavier Garcia ; Hamid, Anis A ; Ottaviano, Margaret ; Palmieri, Giovanella ; Kitson, Robert ; Reid, Alison ; Heng, Daniel Y C ; Bedard, Philippe L ; Sweeney, Christopher J ; Connors, Jean M

Abstract: BACKGROUND It remains unclear which patients with metastatic germ cell tumours (mGCTs) need prophylactic anticoagulation to prevent venous thromboembolic events (VTEs). OBJECTIVE To assess the risk and onset of VTEs stratified by risk factors. DESIGN, SETTING, AND PARTICIPANTS This multi-institutional retrospective dataset included mGCT patients treated with first-line platinum-based chemotherapy. INTERVENTION Patients with prophylactic anticoagulation were excluded. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS A regression analysis was performed to select risk factors for VTEs. The simulated number needed to treat (NNT) and the number needed to harm (NNH) with prophylactic anticoagulation were calculated based on the cumulative incidences retrieved from this study and hazard rates of recently published trials describing the efficacy of prophylactic anticoagulation to prevent VTEs and the risk of bleeding events. RESULTS AND LIMITATIONS From 1120 patients, 121 (11%) had a VTE, which occurred prior to chemotherapy in 49 (4%) and on or after chemotherapy in 72 (6%). Six patients (<1%) had a bleeding event without anticoagulation. After backward regression, the one risk factor for a VTE during or after chemotherapy was the use of a venous access device. The simulated cumulative VTE incidence from prophylactic anticoagulation for patients on or after chemotherapy would translate into an NNT of 45 (95% confidence interval [CI] 36-56) and an NNH of 186 (95% CI 87-506). Limitations are mainly related to the retrospective nature of the study. CONCLUSIONS The mGCTs associated VTEs are most common before and during, but not after, chemotherapy. Avoiding venous access device and/or prophylactic anticoagulation with an acceptable risk-benefit profile may decrease VTE occurring on chemotherapy. PATIENT SUMMARY We found that venous thromboembolic events (VTEs) occur rarely after chemotherapy. Based on experience of prophylactic anticoagulation in other cancers, we conclude that the risk of VTE in men undergoing chemotherapy for metastatic germ cell tumours can be decreased by thromboprophylaxis with a reasonable risk-benefit profile and by avoidance of venous access devices.

DOI: https://doi.org/10.1016/j.euf.2020.09.017

Originally published at:
Fankhauser, Christian Daniel; Tran, Ben; Pedregal, Manuel; Ruiz-Morales, José Manuel; Gonzalez-Billalabeitia, Egon; Patrikidou, Anna; Amir, Eitan; Seidel, Christoph; Bokemeyer, Carsten; Hermanns, Thomas; Rumyantsev, Alexey; Tryakin, Alexey; Brito, Margarida; Fléchon, Aude; Kwan, Edmon M; Cheng, Tina; Castellano, Daniel; Del Muro, Xavier Garcia; Hamid, Anis A; Ottaviano, Margaret; Palmieri, Giovanella; Kitson, Robert; Reid, Alison; Heng, Daniel Y C; Bedard, Philippe L; Sweeney, Christopher J; Connors, Jean M (2021). A Risk-benefit Analysis of Prophylactic Anticoagulation for Patients with Metastatic Germ Cell Tumours Undergoing First-line Chemotherapy. European Urology Focus, 7(5):1130-1136.
DOI: https://doi.org/10.1016/j.euf.2020.09.017

A risk benefit analysis of prophylactic anticoagulation for patients with metastatic germ cell tumours undergoing first-line chemotherapy

CD Fankhauser[1], B Tran[2], M Pedregal[3], JM Ruiz-Morales[4], E Gonzalez-Billalabeitia[5], A Patrikidou[6], E Amir[7], C Seidel[8], C Bokemeyer[8], T Hermanns[1], A Rumyantsev[9], A Tryakin[9], M Brito[10], A Fléchon[11], EM Kwan[2], T Cheng[4], D Castellano[13], X Garcia del Muro[13], AA Hamid[14], M Ottaviano[15], G Palmieri[15], R Kitson[6], A Reid[6], DYC Heng[4], PL Bedard[7], CJ Sweeney[3], JM Connors[16]

Affiliation list

1) University Hospital Zurich, University of Zurich, Zurich, Switzerland

2) Peter MacCallum Cancer Centre, Melbourne, Australia

3) Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

4) Tom Baker Cancer Centre, Calgary, Alberta, Canada

5) Hospital Universitario Morales Meseguer – IMIB. UCAM. Murcia, Spain

6) The Royal Marsden NHS Foundation Trust, London, United Kingdom

7) Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

8) Department of Oncology, Hematology, BMT with Division of Pneumology, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany

9) NN Blokhin Russian Cancer Research Centre, Moscow, Russia

10) Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal

11) Centre Léon Bérard, Lyon, France

12) Department of Oncology, Hospital Universitario 12 de octubre, Madrid, Spain

13) Institut Catala d'Oncologia, Idibell, University of Barcelona, Barcelona, Spain

14) Olivia Newton John Cancer, Wellness and Research Centre, Heidelberg, Victoria, Australia

15) CRTR Rare Tumors Reference Center, Università Degli Studi di Napoli Federico II, Naples, Italy

16) Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Corresponding Author:

Jean M Connors

Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Phone: 617-525-9337, Fax: 617-264-6388 Email: jconnors@bwh.harvard.edu

Keywords: Venous Thromboembolism, Germ Cell Tumour, Testicular Cancer, Deep Vein Thrombosis, Pulmonary Embolism, Venous access device

Acknowledgements: none

Disclosures: This study has been presented as poster at ASCO GU 2020 and EAU 2020.

Word count: 2649, Abstract word count: 298

Abstract

Background: It remains unclear which patients with metastatic germ cell tumors (mGCT) need prophylactic anticoagulation to prevent venous thromboembolic events (VTE).

Objective To assess risk and onset of VTE stratified by risk factors.

Design, Setting, and Participants: This multi-institutional retrospective dataset included mGCT patients treated with first-line platinum-based chemotherapy.

Intervention(s): Patients with prophylactic anticoagulation were excluded

Outcome Measurements and Statistical Analysis Regression analysis was performed to select risk factors for VTE. Simulated number needed to treat (NNT) and number needed to harm (NNH) with prophylactic anticoagulation were calculated based on the cumulative incidences retrieved from this study and hazard rates of recently published trials describing the efficacy of prophylactic anticoagulation to prevent VTEs and risk of bleeding events.

Results and Limitations: From 1,120 patients, 121 (11%) had a VTE with 49 (4%) occurring prior chemotherapy and 72 (6%) on or after chemotherapy. Six patients (<1%) had a bleeding event without anti-coagulation. After backward regression, the one risk factor for VTE during or after chemotherapy was the use of a venous access device. The simulated cumulative VTE incidence from prophylactic anticoagulation for patients on or after chemotherapy would translate into a NNT of 45 (95% confidence interval (CI) 36-56) and a NNH of 186 (95% CI 87-506). Limitations are mainly related to the retrospective nature of the study.

Conclusions mGCT associated VTEs are most common before and during but not after chemotherapy. Avoiding venous access device and/or prophylactic

anticoagulation with an acceptable risk:benefit profile may decrease VTE occurring on chemotherapy.

Patient summary We found that VTEs rarely occur after chemotherapy. Based on experience of prophylactic anticoagulation in other cancers, we conclude that the risk of VTE in men undergoing chemotherapy for mGCT can be decreased by thromboprophylaxis with a reasonable risk:benefit profile and by avoidance of venous access devices.

Introduction

In patients with metastatic germ cell tumors (mGCT) venous thromboembolic events (VTE) are recognized complications[1]. The most recent ASCO Clinical Practice Guideline Update recommends VTE prophylaxis with apixaban, rivaroxaban, or low molecular weight heparins (LMWH) to selected high-risk ambulatory patients with cancer [2]. This update was based on the findings of recent clinical trials including a wide variety of tumour types [3-6]. However, as GCT patients were significantly under-represented in those trials, the risk:benefit analysis in mGCT to justify prophylactic anticoagulation is unknown, especially as there is an associated increased risk of bleeding[7]. We aimed to analyse the cumulative incidence and timing of VTE and bleeding in mGCT patients with and without known VTE risk factors to identify patients most likely to benefit from prophylactic anticoagulation.

Patient and Methods

This retrospective analysis identified men diagnosed with mGCT from 23 institutions in 11 countries treated with first-line platinum-based chemotherapy with curative intent between 1998 and 2015. Patients treated with prophylactic anticoagulation, known history of coagulopathy, or previous VTE were excluded. Baseline variables included age, presence of an indwelling vascular access device, primary tumour site, histology, lactate dehydrogenase (LDH), International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic group and retroperitoneal lymph node (RPLN) size. Long-axis diameter of RPLN was measured in axial cross section from the pre-chemotherapy CT scan as recommended by the American Joint Committee on Cancer (AJCC) staging system and a 3.5cm cut-off was used to dichotomize RPLN size as used previously [8]. Khorana score was calculated using body mass index (BMI), serum haemoglobin, leukocyte count and platelet count; all patients were scored as having testicular cancer [9].

Outcomes

VTE was recorded from 90 days before initial diagnosis up to 180 days after start of chemotherapy. In regression analyses the outcome VTE was defined as any deep-vein thrombosis of the lower or upper limbs, cervical or cerebral veins, pelvic and abdominal veins, pulmonary embolism during or after but not before chemotherapy. The reason to develop a prediction model for VTE during or after but not before chemotherapy was based on the idea that prechemotherapy VTE are already present at initial diagnosis and cannot be prevented and were excluded in previous trials [3, 4]. Similarly, venous access device-related VTEs were not counted as VTE. Bleeding was defined as any symptomatic bleeding.

Statistical Considerations

Risk factors for VTE were selected using a backward selection procedure. The number of factors in the final model was determined based on Akaike information criteria (AIC). Odds ratios (OR) and 95% confidence intervals (CI) were provided. The number needed to treat (NNT) to prevent one VTE event and number needed to harm (NNH) to trigger one bleeding event were simulated as described previously [7]. In brief, the HRs from previous trials can be used to estimate the NNT with the following formula [10]:

$$NNT = \frac{1}{(1 - \text{cumulative incidence})^{\text{HR}} - (1 - \text{cumulative incidence})}$$

As shown in this formula, the NNT is not only influenced by the HR but also substantially driven by the cumulative VTE incidence. Because we assumed that VTE diagnosed before chemotherapy were identified on staging scans and would not be prevented by prophylactic anticoagulation, we used only the cumulative VTE incidence during and after chemotherapy for NNT estimations. Regarding the HR for efficacy and safety needed for NNT and NNH simulation we assumed the same HR as shown in the recent randomised controlled trials CASSINI [3] and AVERT [4] reporting HRs of 0.66 [3] and 0.41[4] for VTE reduction and a HR of 1.96 [3] for increased risk of bleeding. Statistical analyses were performed using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

Of 1,218 patients, 19 were excluded due to coagulopathy, history of VTE or bleeding (Figure 1). The resulting cohort of 1,199 men originated from 23 institutions in 11

countries with a median age of 31 years. The majority of patients had testicular non-seminomatous or mixed GCT and a good prognostic group according to IGCCCG (Table 1).

VTE

Timing and site of VTE in men without prophylactic anticoagulation

In the 1120 men without prophylactic anticoagulation (Figure 1), VTE was diagnosed in 121 (11%) in the following locations: abdominal and pelvic deep vein thrombosis (DVT) in 42 (30%), pulmonary embolism in 39 (28%), lower limb DVT in 25 (18%), upper limb DVT in 11 (8%) unknown locations in 2 (1%), internal jugular thrombosis in 1 (<1%) and cerebral sinus thrombosis in 1 (<1%). Venous access device-related VTEs in 17 men were not counted as VTE. Death as a complication from VTE was reported in 9 (<1%) patients. VTE was diagnosed before chemotherapy in 49/121 (40%), during chemotherapy in 56/121 (46%) and after chemotherapy in 16/121 (13%) patients (Figure 2). Of the 49 patients with VTE before chemotherapy, 34 patients presented with symptomatic VTE, 5 with asymptomatic/incidental VTE and 10 with unknown symptoms.

Cumulative incidence stratified by risk factor

After removing 49 men with VTE before chemotherapy, the cumulative VTE incidence was 72/1071 (7%). The simulated NNT (the number of patients needed to treat with prophylactic anticoagulation to prevent one VTE) would be 26 (95% 21-32) or 5(95% 36-56) depending whether the HR of the CASSINI (0.66) [3] or AVERT (0.41) [4] is used (Table 2). In univariable regression analyses the following risk factors were associated with VTE during or after chemotherapy: IGCCCG intermediate/poor prognostic group, RPLN >3.5cm, use of venous access device, LDH >1.5x upper limit of normal. However, the only variable that remained in a multivariable or after

backward elimination was use of venous access devices (OR 1.8 (95% CI 0.9-3.3) (Supplementary table 1). In men without the risk factor venous access device, the cumulative VTE incidence was 5% leading to a NNT of 32 or 55 depending on the used HR (Table 2). In men with the risk factor venous access device, the cumulative VTE incidence was 10% leading to a NNT of 18 or 31.

Bleeding

Bleeding with full dose anticoagulation

Full dose anticoagulation because of VTE led to bleeding in 5 men (3.6%, 95%CI 1.2%-8.3%) including nose in 2, gastrointestinal in 2 and brain in 1. All 5 required surgical, endoscopic or endovascular procedures and 2 received blood transfusion.

Bleeding with prophylactic anticoagulation

In the 79 men with prophylactic anticoagulation, bleeding occurred in 2 (2.5%, 95% CI 0.3%-8.8%) in the following sites: abdominal in 1 and brain in 1. Surgical, endoscopic or endovascular procedures were not necessary in these patients; one required blood transfusions.

Bleeding without any anticoagulation

In 1,120 men on neither prophylactic nor full anticoagulation bleeding was reported in 6 (0.5%, 95%CI 0.02%-1%) including the following sites: Nose in 2, retroperitoneal in 1, bladder in 1 and unknown sites in 2. All 6 underwent a surgical, endoscopic or endovascular procedure and 3 patients required blood transfusions. The NNH was calculated by taking the cumulative bleeding incidence for men not treated with any anticoagulation (6/1120, 0.05%), and using the observed HR of 1.96 with DOAC prophylaxis (4) to obtain an estimated NNH of 186 (95% CI 87-506) for VTE prophylaxis in men with mGCT.

Discussion

VTE are common complications in patients with cancer [11]. Although previous reports suggested that VTE is associated with shorter progression-free and overall survival [12], the VTE mortality in our cohort was <1% which indicates that VTE prophylaxis would probably also translate in a small survival benefit. Nevertheless, as the majority of patients will be cured after chemotherapy, delay of chemotherapy, long term morbidity and loss of quality of life[13] needs to be prevented in this young patient population. According to our simulations the use of thromboprophylaxis only slightly increases the risks of bleeding but considerably reduces the risk of VTE during chemotherapy.

The recent CASSINI[3] and AVERT[4] trials assessed the risks and benefits of VTE prophylaxis in ambulatory patients selected for increased risk of VTE and receiving chemotherapy using rivaroxaban or apixaban. Both trials demonstrated a 30-60% risk reduction in VTE but increased risk of bleeding, similar to prior findings with LMWH which were in unselected patients with low cumulative VTE rate [5, 6]. Based on the recent results, the ASCO Clinical Practice Guideline Update now recommends offering VTE prophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk outpatients—those with a Khorana risk score $\geq$2 and low risk of bleeding [2]. However, this recommendation is based on clinical trials in which mGCT patients were significantly under-represented and we have previously pointed out that disease specific risk benefit assessments are needed [7]. Therefore, it remains challenging to identify mGCT patients at a sufficiently high risk for VTE to justify prophylactic anticoagulation.

Our results confirm that men with mGCT are at a high risk for VTE prior to and until the end of chemotherapy. The simulated risks and benefits of prophylactic anticoagulation suggest prophylactic anticoagulation prior to and until the end of chemotherapy is a reasonable option for men with mGCT as the cumulative VTE incidence sharply decreases after chemotherapy (Figure 2). Several prior studies described risk factors for VTEs occurring at any time point and did not specific whether VTE occurred before, during or after chemotherapy [14-20]. In our cohort this outcome definition would have confirmed RPLN >3.5cm and Khorana score as risk factors in backward regression (data not shown). However, our analysis was focussed on the setting where prophylactic anticoagulation would be able to prevent VTEs. Specifically, the VTEs occurring during or after chemotherapy as those occurring before chemotherapy were found based on symptoms leading to diagnosis of metastatic disease or on staging scans and cannot be prevented by prophylactic anti-coagulation. Therefore, RPLN >3.5cm and Khorana score are only risk factors for preoperative chemotherapy whereas use of a venous access device remained as the only risk factor for VTE during or after chemotherapy. This more precise VTE definition is therefore the explanation why previously described risk factors for VTEs in general were not selected in our prediction model.

Although prophylactic thromboprophylaxis may only lead to limited absolute risk reduction of VTE, it is important to underline that first, a few patients died because of VTE and second not only VTEs itself but also complications which may follow can be prevented. A direct consequence of VTE include the need for full-anticoagulation which is associated with a higher risk for clinically relevant bleeding as up to 10% of patients on full-anticoagulation for treatment of VTE [21, 22]. Long term complications

from VTE include post-thrombotic syndromes leading to recurring venous leg ulcers resulting in chronic pain, decreased mobility, and ongoing medical resource utilization. Similarly, pulmonary embolism can impair right ventricular function and pulmonary arterial pressure which will not recover in 10–30% of patients, and up to 4% will develop chronic thromboembolic pulmonary hypertension [23]. These complications will further decrease quality of life and increase life time costs to a higher extent then simulated previously [24] as many mGCT patients develop VTEs in their 20s or 30s. Also, if a patient requires post chemotherapy surgery, full dose anti-coagulation presents a management difficulty.

Two simple interventions prevent VTE and the associated complications: First, the restrictive use of venous access devices and second the prescription thromboprophylaxis. The latter either consist of oral thromboprophylaxis (apixaban 2.5 mg bid or rivaroxaban 10 mg q) or subcutaneous LMWH which is for example already standard of care in most German institutions [25].

The proportion of men with asymptomatic VTEs before start of treatment merits further discussion. Similar to CASSINI[3] in which 5% of all patients had pre-existing proximal deep-vein thrombosis before start of treatment, <1% of our cohort presented with asymptomatic and incidentally identified VTEs before starting chemotherapy. Those patients should ideally be identified early on and treated with full anticoagulation instead of prophylactic anticoagulation. Therefore we suggest to (1) specifically ask the radiologist to assess for VTE in the abdomen/pelvis or chest in the staging CT and (2) to investigate the value of venous duplex compression ultrasonography of both legs as a screening tool to identify lower limb DVT in further studies.

The limitations of our analysis include retrospective data collection subject to selection and reporting bias, missing data, heterogeneity in practice patterns, as well as other potential confounders of outcome. Given varying follow-up frequency this study might not have included all consecutively treated patients at all participating centres and missed VTE or bleeding events. Our assumption that the observed HR for VTE risk in other clinical trials can be transferred to mGCT patients and that the relative risk would remain constant across all risk should ideally be confirmed in randomized trials incorporating health economic and quality of life analyses. Similarly, further clarification of bleeding risk in this population treated with prophylactic anticoagulation needs to be assessed. The bleeding risk estimations are supported by our small cohorts on prophylactic anticoagulation and full anticoagulation. However, those are maybe overestimations of major bleeding as epistaxis was counted as bleeding event and prophylactic anticoagulation was probably given to patients with larger volume disease and no standard ascertainment. Nevertheless, it remains unclear whether certain subgroups e.g. men with brain metastases or high volume choriocarcinoma lung metastases may have a higher risk of bleeding. Because the risk of bleeding is crucial for risk benefit assessment further reports of bleeding risk with different anticoagulants or risk factors (e.g. thrombocytopenia) are needed. Additionally, cost-effectiveness analyses to describe the costs of prophylactic anticoagulation as well as need and duration of prophylactic anticoagulation after RPLN dissection needs to be defined.

The first and most important strength of our analysis is the meticulous definition of VTE: as VTEs present before chemotherapy might not be prevented by prophylactic

anticoagulation we excluded all VTE before chemotherapy in our NNT analyses. We also excluded venous access device VTEs as such VTEs often show a more favourable outcome compared to other VTEs. The second strength of our analysis is the sample size in a rare disease allowing multivariable analysis. Given the low incidence of mGCT and rarity of the disease, large prospective randomized trials of VTE prophylaxis are currently not planned and are unlikely to be performed. Therefore, this analysis presents evidence that prophylactic anticoagulation may have a reasonable risk:benefit prophylaxis in all mGCT patients, especially at the time of diagnosis and during chemotherapy.

Figure legends

Figure 1 Patient flow diagram

Figure 2 Histogram with density line describing the occurrence of venous thromboembolic events (VTE) before, during and after chemotherapy.

References

[1] Lauritsen J, Hansen MK, Bandak M, Kreiberg MB, Skøtt JW, Wagner T, et al. Cardiovascular Risk Factors and Disease After Male Germ Cell Cancer. Journal of Clinical Oncology. 2019:JCO.19.01180.
[2] Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology. 2019:JCO.19.01461.
[3] Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. New England Journal of Medicine. 2019;380:720-8.
[4] Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. The New England journal of medicine. 2019;380:711-9.
[5] Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. The New England journal of medicine. 2012;366:601-9.
[6] Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with

metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. The Lancet Oncology. 2009;10:943-9.
[7] Fankhauser CD, Sweeney CJ, Connors JM. Re: Rivaroxaban for Thromboprophylaxis in High-risk Ambulatory Patients with Cancer. European urology. 2019.
[8] Tran B, Ruiz-Morales JM, Gonzalez-Billalabeitia E, Patrikidou A, Amir E, Seidel C, et al. Large retroperitoneal lymphadenopathy and increased risk of venous thromboembolism in patients receiving first-line chemotherapy for metastatic germ cell tumors: A study by the global germ cell cancer group (G3). Cancer medicine. 2020;9:116-24.
[9] Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902-7.
[10] Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319:1492-5.
[11] Connors JM. Prophylaxis against Venous Thromboembolism in Ambulatory Patients with Cancer. New England Journal of Medicine. 2014;370:2515-9.
[12] Gonzalez-Billalabeitia E, Castellano D, Sobrevilla N, Guma J, Hervas D, Luengo MI, et al. Prognostic Significance of Venous Thromboembolic Events in Disseminated Germ Cell Cancer Patients. Journal of the National Cancer Institute. 2017;109.
[13] Kahn SR, Ducruet T, Lamping DL, Arsenault L, Miron MJ, Roussin A, et al. Prospective Evaluation of Health-Related Quality of Life in Patients With Deep Venous Thrombosis. Archives of Internal Medicine. 2005;165:1173-8.
[14] Honecker F, Koychev D, Luhmann AD, Langer F, Dieckmann KP, Bokemeyer C, et al. Venous thromboembolic events in germ cell cancer patients undergoing platinum-based chemotherapy. Onkologie. 2013;36:663-8.
[15] Solari L, Krönig M, Ihorst G, Drognitz K, Heinz J, Jilg CA, et al. High Rates of Thromboembolic Events in Patients with Germ Cell Cancer Undergoing Cisplatin-Based Polychemotherapy. Urol Int. 2016;96:399-405.
[16] Gizzi M, Oberic L, Massard C, Poterie A, Le Teuff G, Loriot Y, et al. Predicting and preventing thromboembolic events in patients receiving cisplatin-based chemotherapy for germ cell tumours. European journal of cancer (Oxford, England : 1990). 2016;69:151-7.
[17] Bezan A, Posch F, Ploner F, Bauernhofer T, Pichler M, Szkandera J, et al. Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. PloS one. 2017;12:e0176283.
[18] Paffenholz P, Grein K, Heidegger I, Nestler T, Grabbert M, Salem J, et al. Predictors of thrombosis in testicular cancer during platinum-based chemotherapy. World journal of urology. 2018.
[19] Piketty A-C, Fléchon A, Laplanche A, Nouyrigat E, Droz J-P, Théodore C, et al. The risk of thrombo-embolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. Br J Cancer. 2005;93:909-14.
[20] Srikanthan A, Tran B, Beausoleil M, Jewett MAS, Hamilton RJ, Sturgeon JFG, et al. Large retroperitoneal lymphadenopathy as a predictor of venous thromboembolism in patients with disseminated germ cell tumors treated with chemotherapy. J Clin Oncol. 2015;33:582-7.
[21] Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in

Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018;36:2017-23.
[22] Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. The New England journal of medicine. 2013;369:1406-15.
[23] Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Reviews. 2014;28:221-6.
[24] Caprini JA, Botteman MF, Stephens JM, Nadipelli V, Ewing MM, Brandt S, et al. Economic Burden of Long-Term Complications of Deep Vein Thrombosis after Total Hip Replacement Surgery in the United States. Value in Health. 2003;6:59-74.
[25] Nestler T, Huber J, Laury AM, Isbarn H, Heidenreich A, Schmelz HU, et al. Thromboprophylaxis and the route of administration of chemotherapy in testicular cancer patients in German-speaking countries. World journal of urology. 2018;36:913-20.
[26] Castellucci LA, Shaw J, van der Salm K, Erkens P, Le Gal G, Petrcich W, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thrombosis Research. 2015;136:727-31.
[27] Johnston N, Bodegard J, Jerström S, Åkesson J, Brorsson H, Alfredsson J, et al. Effects of interactive patient smartphone support app on drug adherence and lifestyle changes in myocardial infarction patients: A randomized study. American Heart Journal. 2016;178:85-94.

Country	
Canada	273 (23%)
Spain	260 (22%)
United Kingdom	152 (13%)
Switzerland	92 (8%)
United States of America	81 (7%)
Italy	74 (6%)
Germany	71 (6%)
Russia	67 (5%)
Australia	53 (4%)
Portugal	49 (4%)
France	27 (2%)
Median age at diagnosis [IQR]	31 [26-38]
Smoking status	
Current smoker	319 (27%)
Ex-smoker	111 (9%)
Never smoker	527 (44%)
Missing	242 (20%)
Median Body mass index (kg/m2) [IQR]	25 [22-28]
Primary site of GCT	
Gonadal	1111 (93%)
Extra-gonadal	84 (7%)
Missing	4 (<1%)
Histology	
Non-seminoma/Mixed	876 (73%)
Seminoma	317 (27%)
Scar	6 (<1%)
IGCCCG Prognosis	
Good	774 (65%)
Intermediate	233 (20%)
Poor	188 (15%)
Missing	4 (<1%)
Chemotherapy	
BEP	917 (76%)
EP	88 (7%)
VIP	24 (2%)
TIP	3 (<1%)
Other	85 (7%)
missing	82 (7%)
Median number of chemotherapy cycles [IQR]	3 [3-4]
Venous access device	
Used	288 (24%)
Not used	634 (53%)
Missing	277 (23%)
Khorana score	
1	752 (63%)
2	237 (20%)
3	70 (6%)

4	9 (<1%)
Missing	131 (11%)
RPLN size	
≤3.5 cm	619 (52%)
>3.5cm	454 (38%)
Missing	126 (10%)
LDH levels	
< 1.5x ULN	728 (61%)
1.5 - 5x ULN	264 (22%)
5 - 10x ULN	57 (5%)
>10x ULN	38 (3%)
Missing	112 (9%)

Table 1 Baseline characteristics of 1199 patients with metastastic germ cell tumors

Abbreviations: IGCCCG: International Germ Cell Cancer Collaborative Group; IQR: Interquartile range from 25-75% percentiles, LDH: lactate dehydrogenase, RPLN: retroperitoneal lymph node, ULN: upper limit of normal

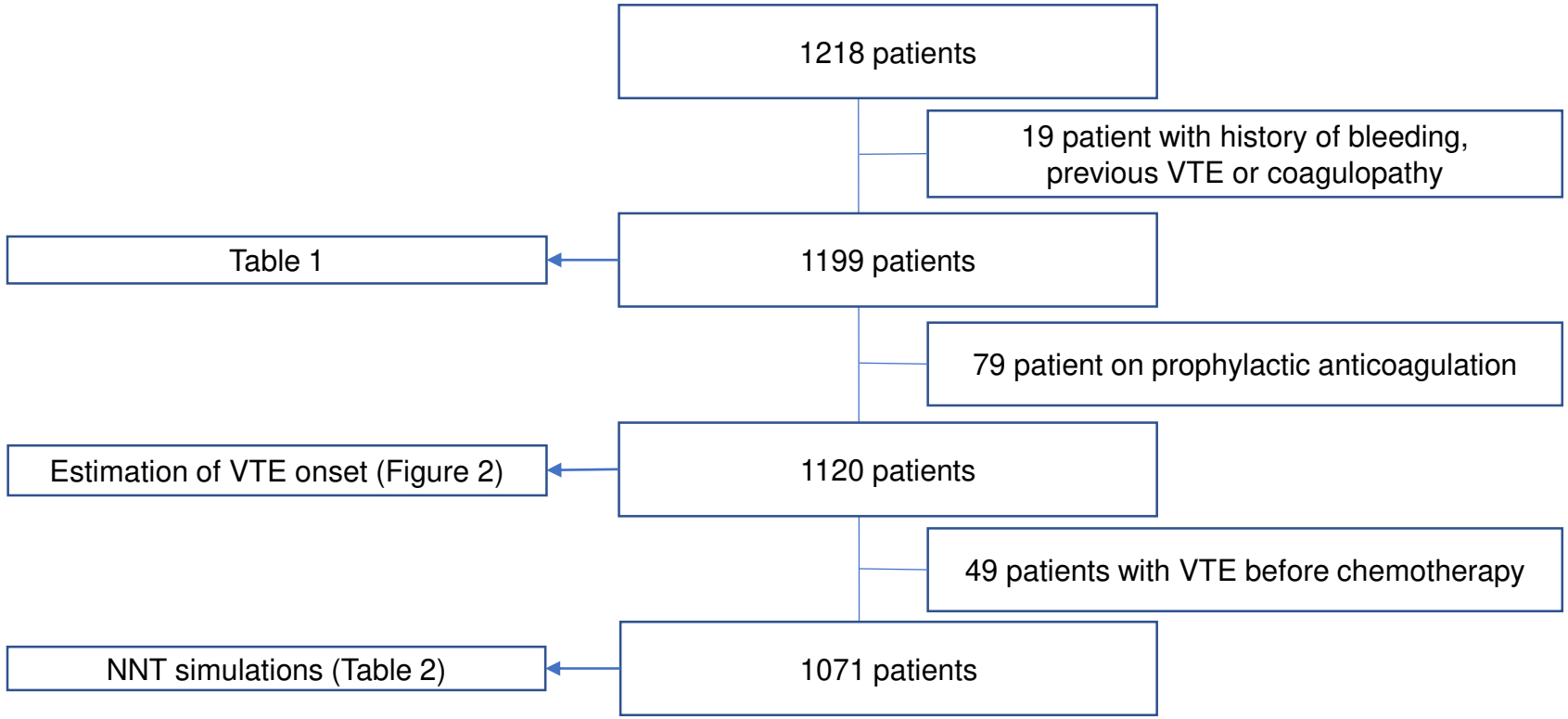
Table 2 Number needed to treat based on observed cumulative VTE incidence in 1071 patients without prophylactic anticoagulation

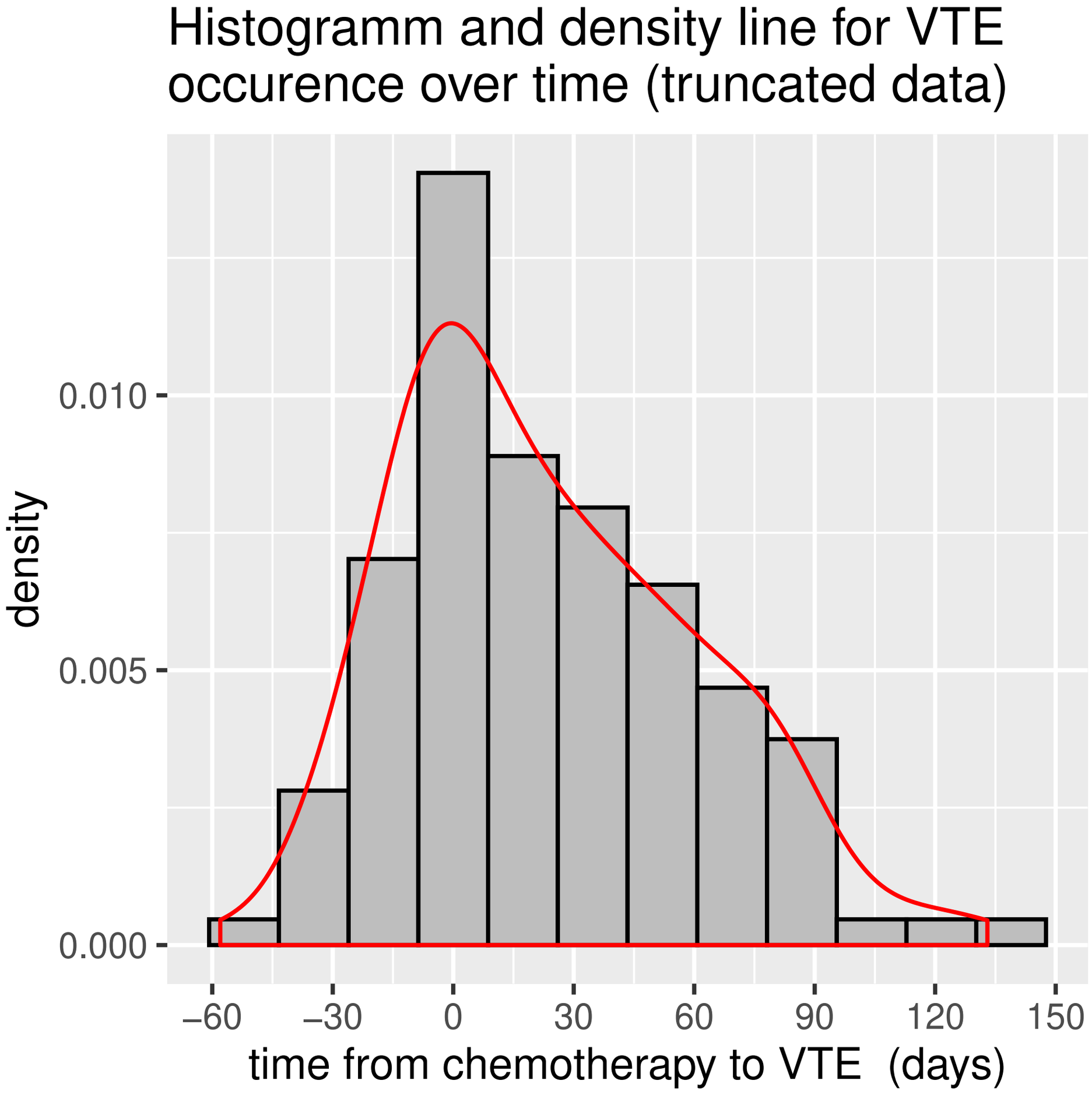
	All patients		Stratified by risk factor				
			No venous access device		Venous access device		Venous access device usage missing
Cumulative VTE incidence* 95% CI	7% (72/1071) 5-8%		5% (31/571) 4-8%		10% (23/234) 6-14%		7% (18/266) 4-10%
NNT using HR of 0.66 95% CI	45 36-56		55 40-80		31 22-47		44 29-73
NNT using HR of 0.41 95% CI	26 21-32		32 23-46		18 12-27		25 17-42

Abbreviations: CI: Confidence interval, HR: Hazard ration, NNT: number needed to treat, VTE: venous thromboembolic events, *defined as any deep-vein thrombosis of the lower or upper limbs, cervical or cerebral veins, pelvic and abdominal veins, pulmonary embolism during or after but not before chemotherapy. Venous access device-related VTEs were not counted as VTE in the regression or further simulation analyses.

Take home message

The results of this study suggest that all metastatic germ cell cancer patients undergoing first-line chemotherapy have an increased risk for VTE, specifically before and during chemotherapy. Avoidance of venous access devices and prophylactic anticoagulation for patients during chemotherapy with an acceptable risk:benefit profile are two simple strategies to possibly decrease VTE risk.


1218 patients
19 patient with history of bleeding, previous VTE or coagulopathy
1199 patients
Table 1
79 patient on prophylactic anticoagulation
1120 patients
Estimation of VTE onset (Figure 2)
49 patients with VTE before chemotherapy
1071 patients
NNT simulations (Table 2)


Histogramm and density line for VTE occurence over time (truncated data)
density
0.010
0.005
0.000
–60
–30
0
30
60
90
120
150
time from chemotherapy to VTE (days)

Variable	Univariable regression		Multivariable regression		Model after backwards regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Khorana Score	1.8 (0.7-4.1)	0.2		0.9		
1-2			Reference			
3-4			1.1 (0.2-3.8)			
RPLN	1.9 (1.1-3.2)	0.02		0.2		0.07
≤3.5cm			Reference		Reference	
>3.5cm			1.7 (0.8-3.6)		1.8 (0.9-3.3)	
Venous access device	1.9 (1.1-3.3)	0.03		0.004		0.02
No			Reference		Reference	
Yes			2.8 (1.4-5.8)		2.1 (1.1-3.9)	
Primary site	2.0 (0.9-4.2)	0.08		0.9		
Gonadal			Reference			
Extra-gonadal			1.0 (0.2-3.0)			
IGCCCG	3.0 (1.7-5.8)	0.01		0.3		
Good/intermediate			Reference			
Poor			1.5 (0.6-3.5)			
LDH	1.9 (1.2-3.2)	0.01		0.8		
<1.5 ULN			Reference			
≥1.5 ULN			0.9 (0.3-2.2)			

Supplementary Table 1 Uni- and multivariable regression analysis of risk factors for venous thromboembolic events during or after chemotherapy

Abbreviations: CI: confidence interval, IGCCCG: International Germ Cell Cancer Collaborative Group, LDH: Lactate Dehydrogenase, OR: odds ratio, RPLN: retroperitoneal lymph node, ULN: upper limit of normal